Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Leslye Davidson on June 29, 2010.

Claim 10 (currently amended): The method of claim 1, wherein the dry powder further comprises ~~further comprising~~ one or more of: a monosaccharide, a disaccharide, and an oligosaccharide.

Claim 11 (currently amended): The method of claim 1, wherein the dry powder further comprises ~~further comprising~~ one or more of: dextran, dextrin, glucose and mannitol.

Claim 13 (currently amended): The method of claim 1, wherein the dry powder further comprises ~~further comprising~~ one or more of: rhDNase, gelsolin and thymosin g4.

Claim 14 (currently amended): The method of claim 1, wherein the dry powder further comprises ~~further comprising~~ one or more of: acetylcysteine and Nacystelyn.

Claim 16 (currently amended): The method of claim 15, wherein the composition has a ~~less than 5 μm~~ fine particle fraction of at least 50%, fine particle fraction being the percentage mass of particles with a size of less than 5μm.

Claim 18 (currently amended): The method of claim 15, wherein the composition comprises~~ing~~ fine particles of ~~at least~~ the one or more mucoactive agents, which have upon their surfaces an amount of the leucine as ~~and~~ a force control agent.

Claim 19 (currently amended): The method of claim 18, wherein ~~the~~ an additional force control agent is selected from the group consisting of: an amino acid peptide ~~or derivatives thereof~~, a phospholipid and a metal stearate.

Claim 20 (currently amended): The method of claim 19, wherein ~~the~~ an additional force control agent is selected from the group consisting of: ~~leucine,~~ lysine, cysteine, and mixtures thereof.

Claim 34 (currently amended): A method as claimed in claim 31, wherein the ~~one or more mucoactive agents are~~ heparin is co-spray dried with ~~a force control agent~~ the leucine.

Claim 35 (currently amended): A method of producing particles for use in a composition

as claimed in claim 1, the method comprising the step of jet milling particles of the ~~one or more mucoactive agents~~ heparin in the presence of an element selected from the group consisting of: air, a compressible gas, and a fluid.

Claim 36 (currently amended): A method as claimed in claim 35, wherein the particles are jet milled in the presence of ~~a force control agent~~ the leucine.

Specification

The following paragraph is inserted at the beginning of the first page of the specification:

Cross-Reference to Related Applications

This application is a national stage application of PCT international application PCT/GB04/03932, filed September 15, 2004, which claims priority to foreign applications GB0321611.6, filed September 15, 2003, and GB0327723.3, filed November 28, 2003.

On p. 6 of the specification, the brief description of the drawings which was added to the specification by amendment on March 9, 2006 is amended as follows:

Brief Description of the Drawings

FIG. 1 How USN works

FIG. 2 Schematic Drawing of Ultrasonic Set-up

FIG. 3 Graph showing the dose-response curve for administration of heparin to CF sputum samples, as measured by the decrease in G* (vector sum of viscosity and elasticity of sputum).

FIG. 4 Graph showing the effect of administration of various heparin preparations to CF sputum samples, as measured by the decrease in G* (vector sum of viscosity and elasticity of sputum). Samples 1 and 2 are heparin disaccharide at 1.6 mg/mL and 5 mg/mL respectively, samples 3 and 4 are heparin polysaccharide at 1.6 mg/mL and 5 mg/mL respectively, and samples 5 and 6 are unfractionated heparin at 1.6 mg/mL and 5 mg/mL respectively.

Detailed Action

This office action is a response to applicant's communication submitted April 27, 2010 wherein claims 1-3, 6-8, 10, 11, 13-25, and 41-48 are amended and new claims 49 and 50 are introduced. This application is a national stage application of PCT/GB04/03932, filed September 15, 2004, which claims priority to foreign applications GB0321611.6, filed September 15, 2003, and GB0327723.3, filed November 28, 2003.

Claims 1-3, 6-8, 10, 11, 13-25, and 30-50 are pending in this application.

Claims 1-3, 6-8, 10, 11, 13-25, and 30-50 as amended are examined on the merits herein.

Reasons for Allowance

Applicant's amendment, submitted April 27, 2010, with respect to the rejection of instant claims 22 and 23 under 35 USC 112, second paragraph, for indefinitely failing to define the abbreviation MMAD, has been fully considered and found to be persuasive to remove the rejection as claims 22 and 23 have been amended to replace the abbreviation with the full-length term. Therefore the rejection is withdrawn.

Applicant's amendment, submitted April 27, 2010, with respect to the rejection of instant claims 1-3, 6-10, 14-28, 30, 40-42, and 44-48 under 35 USC 103(a) for being obvious over Ahmed et al. in view of Staniforth et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to

encompass only the combination of heparin and leucine which is shown to produce unexpected results. Therefore the rejection is withdrawn.

Applicant's amendment, submitted April 27, 2010, with respect to the rejection of instant claims 31-34 under 35 USC 103(a) for being obvious over Ahmed et al. in view of Staniforth in view of Dunbar et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to encompass only the combination of heparin and leucine which is shown to produce unexpected results. Therefore the rejection is withdrawn.

Applicant's amendment, submitted April 27, 2010, with respect to the rejection of instant claims 11 and 35-39 under 35 USC 103(a) for being obvious over Ahmed et al. in view of Staniforth et al. in view of Chickering et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to encompass only the combination of heparin and leucine which is shown to produce unexpected results. Therefore the rejection is withdrawn.

Applicant's amendment, submitted April 27, 2010, with respect to the rejection of instant claim 13 under 35 USC 103(a) for being obvious over Ahmed et al. in view of Staniforth et al. in view of Stossel et al., has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to encompass

only the combination of heparin and leucine which is shown to produce unexpected results. Therefore the rejection is withdrawn.

Applicant's amendment, submitted April 27, 2010, with respect to the rejection of instant claim 11 under 35 USC 103(a) for being obvious over Ahmed et al. in view of Staniforth et al. in view of Trofast, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to encompass only the combination of heparin and leucine which is shown to produce unexpected results. Therefore the rejection is withdrawn.

Currently claims 1-3, 6-8, 10, 11, 13-25, and 30-50 are pending in this application and have been examined on the merits herein. Applicant's amendment submitted April 27, 2010, and the enclosed examiner's amendment, are seen to be persuasive to remove all rejections of record in the previous office action and place the application in condition for allowance. Reasons for allowance are as follows:

The claimed invention is seen to be adequately described and enabled by the specification as originally filed. Therefore the claims meet the requirements of 35 USC 112.

Furthermore the claimed invention is seen to be novel and non-obvious over the prior art. No prior art reference is seen to teach a therapeutic method for treating the claimed conditions comprising administering a combination of heparin and 2% or more of leucine. The closest prior art is the therapeutic method of Ahmed et al. WO99/06025

(Reference of record in previous action) which discloses a method for treating late-phase allergic responses by inhalation of a dry powder comprising ultra-low-molecular-weight heparin. Although the reference discloses that various inert pharmaceutical excipients can be included in the dry powder formulations it does not specifically identify leucine as a pharmaceutical additive. While one of ordinary skill in the art would have been aware of the teaching of Staniforth et al. WO97/03649 (reference of record in previous action) which discloses leucine as a pharmaceutical additive for inhalable powders, Applicant has demonstrated that the addition of 2% or more of leucine to an inhalable heparin powder produces unexpectedly improved results not expected based on the prior art such as Staniforth et al. Specifically, based on table 1 on p. 23 of Staniforth et al., a composition of budesonide with 1% leucine produces a powder having a respirable fraction of 67.3%, while increasing the content of leucine to 5% or 10% decreases the respirable fraction and increases the standard deviation and coefficient of variation. Therefore one of ordinary skill in the art would have regarded leucine to be useful at a concentration of 1%, but would have considered greater concentrations such as 2%, 5%, or 10%, to produce inferior compositions with a lower respirable fraction and a less controllable particle size. However, based on Applicant's specification, particularly the example on pp. 44-45, inclusion of 2-10% leucine in a leucine/heparin formulation produces an increased fine particle fraction. One skilled in the art would have regarded this fine particle fraction as being an indicator of the respirable fraction or effective dosage. Therefore Applicant has demonstrated that the combination of heparin with 2% or more of leucine produces a dry powder with an

unexpectedly increased fine particle fraction based on what would be expected from the prior art, which is effective to overcome any finding of *prima facie* obviousness based on the prior art.

For the same reasons, the instantly claimed invention is not obvious over the generic teachings of any of US patents 6673335, 6518239, or 6372258, (cited in PTO-892) which generically disclose dry powders comprising an active agent and optional additives which can include an amino acid, but do not disclose the specific combination of heparin with 2% or more of leucine.

Therefore the claims meet the requirements of 35 USC 102 and 103.

Still further, although commonly owned US application 10/570902 (pre-grant publication 2006/0292081, cited in PTO-892) claims a method of making heparin/leucine dry powders which can comprise up to 20% of leucine as a force control agent, this application does not claim therapeutic methods for treating the specific pulmonary diseases recited in the instant claims. Furthermore although new claims 49 and 50 recite dry powder compositions which do not require or suggest any specific method of use, no issue of double patenting exists because the claims of 10/570902 are subject to a restriction between the elected group I, drawn to a method of making a dry powder composition, and the non-elected group II, drawn to a dry powder composition for pulmonary inhalation. Therefore the pending claims of 10/570902 cannot raise issues of double patenting with instant claims 49 and 50.

Accordingly, Applicant's amendment submitted April 27, 2010, and the enclosed examiner's amendment, are sufficient to remove all rejections made in the prior office action as discussed above and to place the application in condition for allowance.

Any comments considered necessary by Applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled, "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
7/1/2010